III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Formaldehyde, HCHO, and its derivatives are chemicals used in numerous industrial operations involving the manufacture, formulation, commercial distribution, and production of a variety of products [1]. Selected chemical and physical properties of formaldehyde monomer (FM) are listed in Table XII-1. The utilization of formaldehyde in the United States is summarized in Table XII-2. Clearly, formaldehyde is an important industrial chemical, so that demand, production, and use of formaldehyde should increase.

In the vapor phase, formaldehyde exists as a monomer FM, whereas the chemistry of formaldehyde in aqueous solutions is more complex [1]. An understanding of the basic chemistry of formaldehyde and its derivatives, shown schematically in Figure III-1 and described in Table XII-3, is essential to any discussion of biologic effects.

Reactions of FM with itself, as described by Walker [1], depend primarily upon temperature and concentration. The presence of small amounts of water, metals, or other impurities may significantly accelerate reactions. The anhydrous gas (FM) is stable in the gas phase over the temperature range of 80-100 C, but undergoes polymerization upon condensation and cooling. Formaldehyde in alcohol and/or water solutions (FS) slowly polymerizes, forming paraformaldehyde and amorphous higher polymers of polyoxymethylene (PF). Amorphous polyoxymethylenes containing 100 residues or more are derived from FM and are regarded as alpha-polyoxymethylenes (PO alpha). PO alpha may be formed by addition of sulfuric acid to FS or PF.

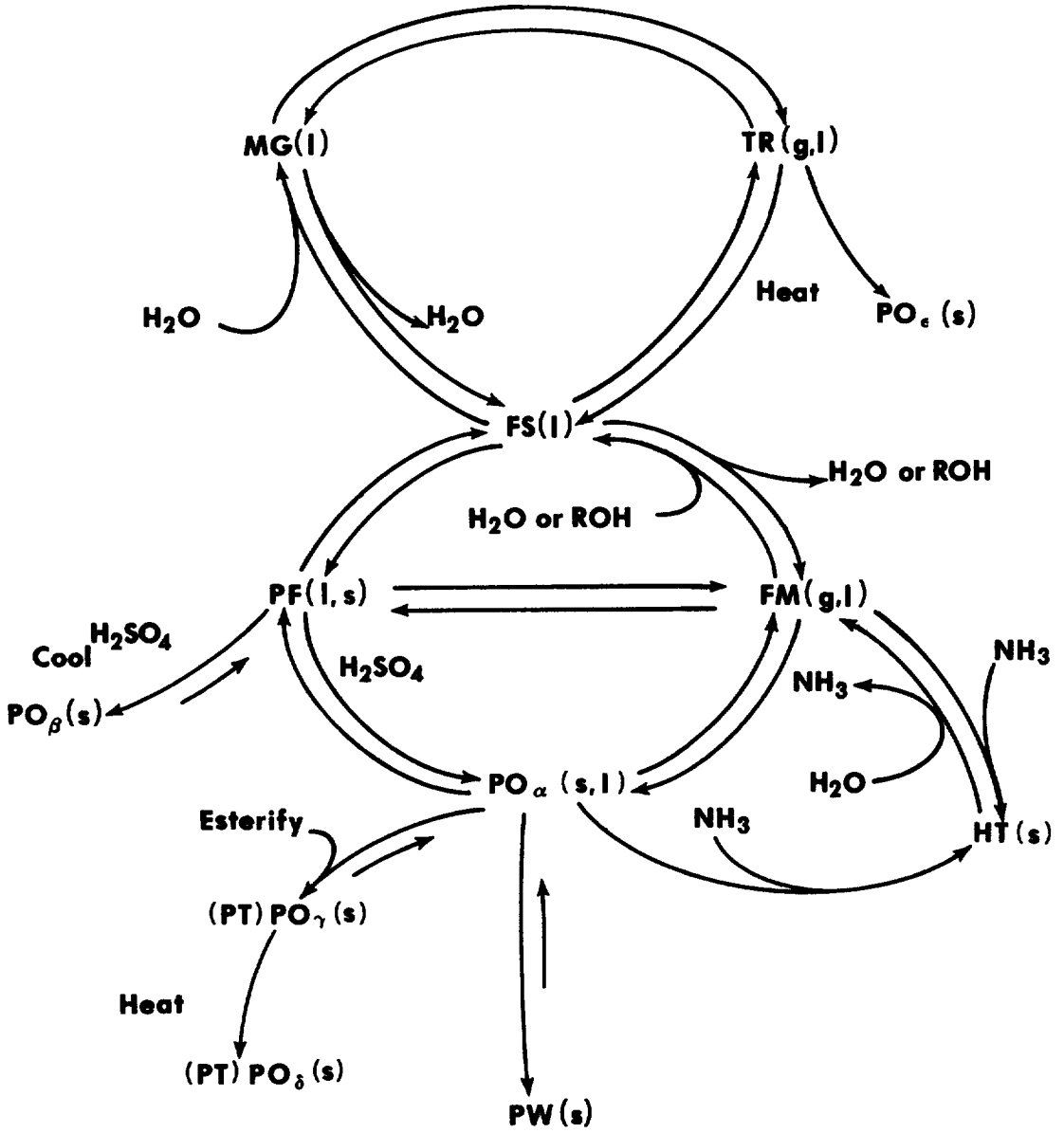

FIGURE III-1

FORMALDEHYDE REACTIONS AND PRODUCTS

FM - Formaldehyde monomer
FS - Formaldehyde in solution
MG - Methylene glycol
PF - Paraformaldehyde
TR - Trioxane
HT - Hexamethylene tetramine
PO - Polyoxymethylenes
PT - Polyoxymethylenes modified
PW - Polyoxymethylenes, high polymers

Slow addition of H2SO4 at 0-5 C produces a highly ordered clear-crystalline polyoxymethylene (PO beta). Esterification of PO alpha yields a relatively stable amorphous product which undergoes rearrangement on heating to various temperatures and forms polymeric ethers and esters (PT), including PO delta. With continued reaction, higher molecular weight insoluble polyoxymethylenes may be formed and are designated as PW. Repeated distillation of the cyclic trimer, trioxane, yields a polyoxymethylene residue, PO epsilon. PO alpha is labile to degradation yielding FM on destructive distillation or on dissolving in alcohol or water. Other PO derivatives are more resistant to degradation and are not generally regarded as sources of FM.

Formaldehyde exists in freshly prepared aqueous solutions as a monohydrate form, methylene glycol (MG) (See Figure III-1). Depending on the age and concentration of the solution, a series of paraformaldehyde and low molecular weight polyoxymethylene glycols (PF) having the typical formula, HO(CH2O)xH, may be present. Lower concentrations of formaldehyde favor formation of methylene glycol as the principal molecular species while higher concentrations and aging of the solutions favor formation of polymeric forms of formaldehyde (PO, PT, PW). Aqueous solubility of the higher polymers decreases with increasing molecular weight, resulting in precipitation of the higher polymers (PO, PT, PW) from solution. To prevent or retard continued polymerization, methanol or other alcohols may be added to formulations as stabilizers. Aqueous solutions of formaldehyde generally contain less than 0.1% FM. However, distillation of such solutions yields a vapor that consists primarily of unhydrated FM in equilibrium with a low concentration of MG vapor [1]. Although FM is not found in significant amounts in solid or liquid products, formulations, or

derivatives, vapor produced by, or evolved from, such materials may contain significant amounts of FM gas. Distillation of an alkaline solution containing polymeric aldehydes derived from formaldehyde is a fundamental process for obtaining or recovering FM.

The number of employees engaged in the direct production of formaldehyde monomer, supplied as an anhydrous product or in solution, has been estimated by NIOSH to be 8,000. Formaldehyde is used (see Table XII-4) in the manufacture of a variety of derivatives, including phenolic resins, urea-formaldehyde resins, polyacetal resins, melamine, pentaerythritol, hexamethylenetetramine, fertilizers, and acetylene derivatives. Some of these materials may contain unreacted formaldehyde residues or yield formaldehyde on decomposition. The population of employees potentially exposed to formaldehyde or substances acting as sources of formaldehyde is uncertain. Although an estimated 8,000 employees may be at risk of exposure to the high concentrations found in industrial synthesis, formulation, and distribution of concentrated products, the numerous uses of formaldehyde and its derivatives indicate that a substantially larger population of employees may be at risk from intermittent exposures to products containing sources of formaldehyde or its congeners and derivatives.

Commercial production of formaldehyde is accomplished by a variety of techniques, including controlled oxidation of low molecular weight aliphatic petroleum hydrocarbons [2] and oxidation of methanol in the presence of a metal catalyst [1,3,4,5]. Two basic techniques for the production of formaldehyde by oxidation of methanol are operation of the process in either a fuel-rich mode or a fuel-lean mode. Other variations

in the oxidation processes are related to differences in catalyst and the extent to which off-gases are recirculated.

Formaldehyde gas has a characteristic pungent odor. The pure, dry gas is stable in the temperature range of 80-100 C [1]. At usual room temperatures, polymerization occurs slowly and produces a white film of polyoxymethylene on the walls of containers, while cooling to temperatures between -20 to -80 C can cause condensation and more rapid polymerization. Table XII-3 lists the composition, properties, and structures of various formaldehyde polymers described by Walker [1]. Stability of the monomer depends on purity. Even traces of polar compounds (water, acids, or bases) can accelerate polymerization [2]. Water is a usual contaminant.

Commercial preparations of formaldehyde are available in grades of methanol free, methanol stabilized (NF), or reagent. In addition to methanol or other alcohols, commercial preparations may contain formic acid [6]. Aqueous solutions consist of 0-15% alcohol (methyl, propyl, n-butyl, or isobutyl) [7,2,6] in water containing 30-50% dissolved formaldehyde by weight, which is introduced as a gas consisting of FM. Formaldehyde solutions are supplied in glass carboys of 5- to 13-gallon capacity, lined steel drums of 5- to 50-gallon capacity, 55-gallon stainless steel drums, lined wooden barrels, stainless steel or lined tank trucks of 2,000- to 3,000-gallon capacity, or 8,000- to 10,000-gallon tank cars. In the industrial setting, it is possible to encounter formaldehyde in a variety of containers, processes, and products. One product, hexamethylenetetramine (HT), (CH2)6N4, which is formed by reaction of formaldehyde with ammonia, reacts as formaldehyde in many instances and is regarded as a special form or source of formaldehyde in industrial use [1]. Occupational groups at risk from formaldehyde exposure are listed in Table XII-5.

Although a substantial number of individuals may be intermittently exposed to formaldehyde or substances acting as a source of formaldehyde gas, a relatively smaller number of employees engaged in primary production, formulation, and distribution operations are at comparatively higher risk of incurring occupational exposure by either inhalation or skin and eye contact.

Historical Reports

The preparation and identification of several aldehydes had been elucidated by mid-19th century but the first member of the aldehyde family was unknown. Butlerov prepared formaldehyde in 1859 while attempting a synthesis of MG through hydrolysis of methyl acetate [1]. He also prepared polyoxymethylene using two procedures: by reaction of either methylene iodide with silver oxalate or of methylene iodide with silver oxide. Reaction of the polymeric products with ammonia yielded a crystalline product, hexamethylenetetramine (HT). However, Hofmann [8] reported the direct synthesis and definite identification of formaldehyde in 1867, when he passed a mixture of methanol and air over a heated platinum spiral. This method is a direct forerunner of a modern method of manufacture.

In 1913, Brunnthaler [9] noted that as early as 1893 Blum [10] had shown that formaldehyde combines with proteins. Subsequently, other investigators, Benedicenti [11] in 1897, Sollmann [12] in 1902, Kendall [13] in 1927, Gubareff and Bystrenin [14] in 1932, and Zipf and Bartscher [15] in 1933 demonstrated that formaldehyde combines with specific amino acids.

Formaldehyde reacts with terminal hydrogen atoms, particularly in free amino groups of amino acids. Hydroxymethylated derivatives are formed, which then may interact with other terminal hydrogen atoms by elimination of water and crosslinking in protein chains [16,17]. Stewart [18] showed that red blood cells treated with formaldehyde at 0.2% in solution lost the ability to take up oxygen but retained normal permeability to ammonium chloride and normal impermeability to sodium chloride. A more concentrated solution of formaldehyde (4%) destroyed the selective permeability of the red blood cells presumably produced by crosslinking of protein chains and opening pores in evelopes of the red blood cells.

Ingestion of formaldehyde has resulted in headache, upper gastrointestinal pain [19-23], allergic reactions [19], damage to tissues of the upper gastrointestinal and respiratory tracts [21, 22,24,25], systemic damage [22-24], and death [21,22,26].

In 1904, Levison [26] reported that a person who swallowed 2-3 oz of a "commercial" formaldehyde solution collapsed and died 20 minutes later. At autopsy, the mucosa of the lower esophagus, stomach, and duodenum were dark brown and hardened, and there was an excessive amount of mucus in the bronchi.

The US Department of Agriculture [19] investigated the use of formaldehyde as a food preservative in 1909. Eleven male volunteers received daily 100 mg of formaldehyde in milk for 5 days followed by daily doses of 200 mg of formaldehyde in milk for the next 10 days. During the 15-day test period, one subject stopped taking the formaldehyde after the 11th day, when he took a 100-mg dose, while two others took only 100 mg on the 14th day and nothing on the 15th. Ten of the 11 subjects complained of

stomach or intestinal pain and headache during the test period and for 10 days after their last dose. A burning sensation in the throat and a slight decrease in body temperature were noted in "the majority of cases." A distinct itching rash appeared on the chest and thighs of four of the subjects. This observation was perhaps the earliest evidence of a systemically induced skin reaction to formaldehyde.

In 1909, Bower [23] reported a case involving a 20-year-old woman who swallowed about 0.5 oz of formalin (37-40% aqueous formaldehyde solution). A stomach lavage was performed before the victim collapsed and lost consciousness. The woman regained consciousness after administration of strychnine and later complained of pain in the throat and paroxysmal pain in the stomach. Kidney damage, as evidenced by analysis and physical appearance of the urine, was slight. A diuretic mixture containing about 130 mg each of potassium acetate and potassium citrate was given every 2-4 hours. Recovery was complete after 4 days.

Ely [21] reported in 1910 a case of formaldehyde poisoning that resulted in the death of a child who had ingested a few drops of a 40% formaldehyde solution. At post-mortem examination, the mucous and submucous coatings of the epiglottis, larynx, and trachea were thickened. Upper respiratory tract damage appeared to be a result of direct contact of formaldehyde with tissues at the juncture of the epiglottis and the esophagus and infiltration of the irritant into the trachea.

Earp [24] in 1916 reported three cases of formaldehyde ingestion involving adults. One man who drank 1.5 oz of formalin became cyanotic and cold and vomited. Mucous membranes of the mouth and throat were dry and white. The patient had a weak, irregular pulse, and his respiration was shallow. He was given a quart of milk and periodic injections of various

respiratory and cardiac stimulants. Recovery occurred in 4 days. Ingestion of 0.5 oz formalin by another man produced very little cyanosis, and only a dry, sore throat, and vomiting. The victim recovered after a stomach washing with milk of magnesia, dilute ammonia water, and later a quart of milk administered by means of a stomach tube. A woman who attempted suicide by drinking 4 oz of formalin showed signs of cyanosis, reduced body temperature (96 F), shallow respiration, and a weak, rapid, and irregular pulse. She improved rapidly following administration of an oral dose of dilute ammonia water and injection of strychnine sulfate. Recovery occurred in 4 days.

In 1925, Kline [22] presented 12 fatal case histories from his own files and from those of other physicians, listing clinical treatments and pathologic changes as a result of formaldehyde ingestion. The amount of formaldehyde ingested varied from "a few drops" to 7.5 oz of solutions containing various concentrations of formaldehyde. Pathologic examinations revealed damage that was severe in the lower esophagus and even more extensive in the stomach. Damage produced in these organs varied from hardening of the tissue to extreme corrosion. Congestion, edema, tissue erosion, and hemorrhage were frequently observed, particularly in the lower esophagus. The author noted that, in cases in which victims died 13 hours or more after ingestion of formaldehyde, degenerative changes involving slight cloudy swelling, fatty degeneration, and necrosis in the parenchymatous organs were seen.

Vinson and Harrington [25] reported a case of corrosive stenosis of the stomach in a 59-year-old man caused by the accidental ingestion of formaldehyde. He experienced severe epigastric pain for 2-3 hours after swallowing the solution and was able to ingest only soft foods for about 10

days after the accident. Thereafter, swallowing even of fluids became impossible for 4 days before he entered the hospital. Surgery was performed to bypass the pyloric sphincter and to form an opening into the stomach near the cardiac sphincter. After 2 months of treatment to dilate a stricture below the cardia, the patient was able to swallow any type of food and was permitted to return home. The authors commented that additional dilations of the stricture just below the cardia probably would be needed.

Inhalation of formaldehyde has caused severe irritation of the upper respiratory tract [27,29] and death [27]. In 1934, Böhmer [27] reported that exposure to high concentrations of formaldehyde gas may lead to pulmonary edema. In one case, respiratory paralysis and death occurred within 15 minutes after drinking a 30% solution of formaldehyde. Pulmonary edema from inhalation of formaldehyde appears to be an uncommon response. Respiratory embarassment from acute inflammatory edema of the larynx is the most usual result [28].

In a 1935 report, Krans [29] described a case of chronic exposure to fumes and vapor produced during hot molding of formaldehyde-base synthetic resins. During the parting of 2-piece molds, a cloud of dense, acrid fumes containing "various amounts" of formaldehyde gas was released and, at times, caused immediate throat irritation. Airborne formaldehyde concentrations, durations of exposure, and analyses for other irritants were not reported. Six years earlier, Krans had encountered a man who had been working a short time in a hot molding operation and had acquired a slight cough. Over the next few months, the worker developed a typical bronchial cough. Between 1929 and 1932, the coughing gradually worsened. In 1932, he was suddenly taken ill with what the attending physician diagnosed as

pneumonia. The author concluded that the condition was actually secondary bronchopneumonia caused by the progressive irritant damage resulting from the prolonged mixed exposure to vapor and dust containing formaldehyde at excessive concentrations. Airborne formaldehyde and dust concentration in the plant were not reported.

Prior to 1945, the bulk of the literature describing the effects of short- and long-term contact of the skin with formaldehyde was published in Germany [30-40]. The dangers resulting from the contact of formaldehyde with the skin and nails were summarized in a review article by Chajes [41] published by the International Labour Office in 1930. Individual differences in susceptibility to formaldehyde were noted. Some individuals adapted to exposure, others became progressively more sensitive. Prolonged use of 2-10% formaldehyde solutions produced eczema on the fingers and hands which were covered with vesicles, fissures, and ulcerations; these could eventually extend to the skin of other parts of the body [41]. Erythematous rash and urticaria were reported in some cases. Chajes mentioned a 1922 report from the Medical Inspector of Factories in Great Britain in which dermatitis was said to appear among workmen polishing celluloid substitutes containing 0.015% formaldehyde. Similar cases arising from the industrial use of dilute (less than 0.5%) formaldehyde solutions and pastes were noted. Fingernails, after prolonged contact with formaldehyde, showed a tendency to become brown, to soften, and to decay, while the skin folds of the fingers became inflamed, with suppuration at the site. In other cases, nails became scaly and friable prior to the appearance of inflammation. Occasionally, the fingertips developed a sensitivity which was accompanied by a "tightening pain," extending up to the arms in some cases.

Effects on Humans

(a) Respiratory Tract Irritation

Respiratory tract irritation has been observed after inhalation [42-54] and ingestion [55,56] of formaldehyde. Irritation after inhalation has produced localized effects in the nose [42-47,57-59], the throat [42-45,47-51], and tracheo-bronchial tree [43,47,48,59]. Cases involving respiratory irritation following ingestion [55,56] were due to invasion of the formaldehyde via the glottis.

Ettinger and Jeremias [44] noted eye, nose, and throat irritation in cutters, sewers, and other employees handling nylon fabric coated with urea-formaldehyde resins. These symptoms were attributed primarily to formaldehyde gas present in the workroom in concentrations of 1-11 ppm and secondarily to the contamination of employees' hands with tiny flakes of resin during handling. In the latter case, subsequent rubbing of the eyes with the hands caused irritation and conjunctivitis. In such cases, flakes which had become imbedded in the skin had to be removed by a physician. They also noted that gaseous formaldehyde was released from the fabric during curing and storage, but airborne concentrations of formaldehyde were not reported. The authors concluded that the ideal method for the elimination of the health hazard was improvement of the curing system to achieve complete polymerization in as short a time and at as low a temperature as possible.

In 1957, Zannini and Russo [48], as part of a study of irritant gases, examined a man who had undergone a single acute inhalation of formaldehyde. The patient complained of dyspnea, asthma attacks, asthenia, weight loss, and nervousness. An initial chest radiograph showed accentuated bilateral bronchiovascular markings. Clinical examination

revealed pulmonary edema with diffuse harsh respiration, a 40% decrease in vital capacity, a maximum loss of pulmonary ventilation of 45%, an enlarged left atrium, an accentuated second pulmonary sound, and hyperthyroidism. A second radiograph made 5 months later revealed that the left and right atria and the right ventricle were enlarged. Diaphragmatic hypomobility was also noted at this time. An electrocardiogram showed slight signs of atrial overloading and an intraventricular conduction defect.

Sim and Pattle [46] reported the effects of possible smog irritants on 12 male subjects, all healthy and ranging in age from 18 to 45 years. The men were exposed simultaneously to 13.8 ppm (17.0 mg/cu m) of formaldehyde for 30 minutes in a 100-cu m chamber. No restrictions were placed on their activities; they were allowed to walk around and smoke if they wished to do so. Airborne formaldehyde was generated by bubbling air through a formaldehyde solution. The concentration of formaldehyde in the chamber air was determined as total aldehydes by passing air from the chamber through hydroxylamine hydrochloride at pH 4.5 and determining the amount of HCl liberated by titration with base back to pH 4.5. Formaldehyde at 13.8 ppm produced considerable nasal and eye irritation when the men first entered the chamber, but produced no severe effect despite continued slight lacrimation. The eye irritation was not severe and wore off after about 10 minutes in the chamber. Thus, this study provided some evidence of short-term human adaptation to an irritant stress.

Bourne and Seferian [42] in 1959 reported complaints of burning and stinging eyes, headaches, and nose and throat irritation by customers and employees in several dress shops. The odor was described as suffocating. Complaints were most numerous when the ambient temperature was the highest.

Air sampled in the dress shops was found to contain 0.13-0.45 ppm formaldehyde. Samples of apparel from these same shops contained 5-8 mg of formaldehyde for each 10 g of rayon textiles and 3.4 mg/10 g of cotton, while a wool dress was found to be formaldehyde-free. The authors recommended a ventilation rate of 15 air changes/hour for the shops to remedy the situation.

Glass [49] reported in 1961 that breathing-zone concentrations of 16-30 ppm formaldehyde, as determined by detector tubes, produced irritation of the throat and smarting of the eyes in an unspecified number of the 60 employees in a resin-manufacturing and paper plant. Sixteen workers also had dermatitis with marked erythema of the face and neck. Five of the 16 had edema of the eyelids. Two of these five did not handle the resin but were exposed to both airborne resin dust and formaldehyde gas.

In 1961, Morrill [50] published the results of a study of exposure to formaldehyde in a paper-conditioning installation. Two employees were exposed to airborne formaldehyde released from paper treated with either urea-formaldehyde or melamine-formaldehyde resin. Samples of air taken in the area of the employees' breathing zone contained 0.9-1.6 ppm formaldehyde. No further details as to the number of air samples or the analytical methods used were reported. The employees complained of itching eyes, dry and sore throats, disturbed sleep, and unusual thirst upon awakening in the morning. This report does not take into account, however, the fact that during the work operation one employee stood partially in a ventilated booth housing the paper dryer which may have altered that employee's exposure.

Hovding [45] reported complaints of dryness and irritation of the nose and throat, a burning sensation in the eyes, and itching eruptions of

the skin of the face, neck, and forearms in four women exposed to pyrolysis products generated by thermocutting of polyethylene. The four women presented mild dermatitis, primarily in the vicinity of the eyes, and also on the neck and volar areas of the forearms. Formaldehyde and acrolein were identified as two of these pyrolysis products. The employees also noted feelings of drowsiness and headache at the end of the working day. These last two symptoms and the nose, throat, and eye irritation disappeared during absences from the workplace, but recurred on resumption of work. The employees had been engaged in thermocutting for 1.5 years. They had no histories of previous skin diseases. Occasionally, other employees in the room complained of discomfort from the smoke, so that the cutting operation had to be stopped. One woman working next to the cutting machine showed no clinical signs of dermatitis but, along with the four women employed at the thermocutting operation, gave a positive patch test to a 4% formaldehyde solution.

In 1968, Shipkovitz [58] reported the findings of an investigation of eight textile plants in which formaldehyde was released from fabrics treated with formaldehyde-containing resins. Thirty-two samples of air were examined for formaldehyde by drawing air through fritted bubblers containing sodium bisulfite at the same times that air was drawn through 32 detector tubes. All but two of the detector tube samples failed to detect any formaldehyde (limit of detection either 0.5 or 2 ppm, depending upon which tube was used); the two positive tubes yielded results that were considerably different from those obtained with the bubbler samples. Bubbler samples were analyzed for total aldehyde by iodometric titration, using a method which has a limit of detection of 0.5 ppm but which is not specific for either formaldehyde or total aldehyde. Shipkovitz reported

airborne formaldehyde concentrations of 0-2.7 ppm, with an average of 0.68 ppm. Annoying odor, constant prickling irritation of mucous membranes, heavy tearing, wheezing, excessive thirst, and disturbed sleep were reported by the employees. Based upon "composite estimates" obtained from plant records, interviews with plant foremen, management, and several employees at each plant, the prevalence of respiratory illness and complaints was over 15% for four plants and 5-15% for the other four. The author [58] also mentioned that upon entering certain plant areas an odor was detected immediately which would decrease in intensity as he spent time in the area, but would occur again the next day. This report of olfactory adaptation to formaldehyde is consistent with the observations of Sim and Pattle [46].

In 1975, Kerfoot and Mooney [52] surveyed six funeral homes using formaldehyde and paraformaldehyde in the embalming process. The average concentrations in the air of the embalming rooms were 0.25-1.39 ppm formaldehyde while the total range for all samples was 0.09-5.26 ppm. Formaldehyde exposures were determined by sampling air at a rate of 1.5 liters/minute through a single midget impinger containing 10 ml of 0.1% chromotropic acid in concentrated sulfuric acid until a purple color was obtained. The color intensities of the sampling solutions were read on a recording spectrophotometer. This method is specific for formaldehyde but may have been in error on the low side because the paraformaldehyde could have dissociated to formaldehyde before collection. No prefilter was used. Separate samples of airborne paraformaldehyde dust were collected with a thermal precipitator, and dust particles were sized microscopically. The airborne dust was found to have a geometric mean particle size of 1.6 μm. The investigators noted eye and upper respiratory tract irritation in some

employees at "most" establishments, but this may have been due partly to paraformaldehyde and partly to formaldehyde adsorbed on the dust. The investigators also experienced irritation which wore off within an hour while they remained in the room but reappeared after lunch away from the establishment or upon returning to it on the next day.

The authors also noted that employees other than the embalmers might be severely irritated when entering a room in which an embalmer was working. The investigators suggested that the embalmers become "inured to the vapor" as concentrations gradually increased with time, and that such chronic exposures may contribute to lung diseases. However, they offered no proof for the latter hypothesis.

In a 1966 study [53] of a clothing store, the California Department of Public Health reported airborne work zone concentrations of 0.9-3.3 ppm formaldehyde. The investigators sampled for formaldehyde in air with fritted midget absorbers, containing a solution of 3-methyl-2-benzothiazolone hydrazone hydrochloride (MBTH), for 15-minute periods and analyzed the contents colorimetrically. This method is sensitive to formaldehyde at low concentrations but responds also to other aldehydes. The only aldehyde likely to have been present was formaldehyde. Odors attributed to formaldehyde were noticeable and were accompanied by complaints of mild eye irritation. The investigators postulated that allergies, chronic respiratory diseases, or any preexisting respiratory ailments in employees might be aggravated by such airborne exposures to aldehydes.

The California Department of Public Health conducted another occupational health study [54] in the same year at a textile garment factory where "perma-press" clothing was manufactured. The odor of formaldehyde

was readily noticeable to the observers and was accompanied by eye and upper respiratory tract irritation. Air was drawn through Greenburg-Smith impingers containing sodium bisulfite solution. The method of analysis used, given the large volume of air required in using Greenburg-Smith impingers, provided adequate sensitivity but was a measure of total aldehyde. Again, formaldehyde was probably the only aldehyde present. The airborne formaldehyde concentrations ranged from 0.9 to 2.7 ppm. The greatest discomfort, tearing of the eyes and irritation of the nasal passages and the throat were reported by the employees in areas where the largest quantities of partially completed garments were accumulated. The irritant effects were greatest at the beginning of the workday and after the lunch period. Irritation lasted for about 15-20 minutes during these two periods after which the formaldehyde became tolerable. This study reinforces the observations of Shipkovitz [58] and Kerfoot and Mooney [52] that any "acclimatization" to formaldehyde lasted for no more than a few hours and that irritation returned after a 1-2 hour interruption of exposure.

Porter [59] experienced acute respiratory distress after working with formalin. As a neurology resident, he spent 2 hours preparing brain specimens and inhaled high concentrations of formaldehyde gas. The previous week, he had been exposed to formaldehyde gas for 15 hours. After his more recent exposure of 2 hours, he developed dyspnea and tightness of the chest which became progressively worse during a 15-hour period. His wife noticed an odor of formaldehyde on his breath. Immediately before onset of respiratory distress, there were unpleasant effects on the conjunctivas and nasal mucosa. On hospitalization, the patient was dyspneic. A radiograph of his chest was interpreted to indicate an

inflammatory reaction in his lungs with early edema. Isolated occasional rhonchi where noted and soft diffuse rales were heard over both lung fields. Porter was known to be atopic to a wide range of allergens, and the respiratory distress could have been due to a hypersensitivity reaction but more likely was an acute chemical pneumonitis provoked by formaldehyde. The author suggested that inhalation of formaldehyde gas may entail serious danger to susceptible individuals.

In a study reported by both Yefremov [47] and Zaeva et al [51], 278 employees working in wood-processing plants were examined medically. One hundred twenty-nine (78%) were found to have signs of upper respiratory tract irritation, including hypertrophic, inflammatory, subtrophic or atrophic rhinitis. Airborne formaldehyde concentrations of 2.6-11 mg/cu m (2.1-8.9 ppm), with a maximum of 36.3 mg/cu m (31.2 ppm), produced illness in 39.1-66.2% of those exposed. [51] Airborne formaldehyde concentrations of generally 0.6-4.1 mg/cu m (0.5-3.3 ppm), with a maximum of 8.8 mg/cu m (7.1 ppm), produced an illness rate of 14.6-37.5% [51]. A control group of 200 individuals of corresponding ages had an incidence of respiratory catarrh of 8.9% [51]. Yefremov [47] further noted that signs of chronic respiratory tract irritation were most pronounced in persons 30-59 years of age and in those who had worked for less than 5 years. He further noted that pronounced morbid states developed from inflammatory phenomena in the mucosa of the upper respiratory tract consequent to inhalation of formaldehyde vapor. Initial signs indicating onset of inflammatory pneumonia were: (1) increased travel time of carbon particles from the nares to the nasopharynx (2) more rapid absorption of noratropine from a tampon inserted into the nasal cavity, and (3) decreased olfactory activity for such substances as rosemary, thymol, camphor, and tar.

Zaeva et al [51] also mentioned a study by A. K. Sgibnev without stating where the original information was published. Sgibnev's study reported that particularly sensitive individuals exposed to 1 mg/cu m (0.8 ppm) formaldehyde developed irritation of the mucous membranes of the upper respiratory tract and eyes, respiratory disorders, changes in the function of the autonomic nervous system and enhancement of the alpha-rhythm of the EEG. All perceived the odor.

In 1971, Kratochvil [43] evaluated the health status of employees engaged in the processing of textiles impregnated with urea-formaldehyde and melamine-formaldehyde resins. Airborne formaldehyde concentrations in the workshop did not exceed 5 mg/cu m. The employees complained of irritation of the conjunctivas, nasopharynx, and skin. Objective findings were catarrhal conjunctivitis in 72% of the employees, inflammatory rhinitis in 28%, slightly reddened, dry facial skin in 11%, and chronic bronchitis in 22% of the employees. The author stated that the frequency of occurrence of bronchitis did not differ from that in the general population.

(b) Gastrointestinal Irritation

Ingestion of formaldehyde solutions has caused irritation [55,56,60-62] and damage [55,56,61,62] to the tissues of the gastrointestinal tract and has been responsible for at least 13 deaths [15,21,26,55].

Rathery et al [55] reported in 1940 that a 27-year-old man died 45 minutes after the drinking of 150 cc of 40% formaldehyde. Death was caused by edema of the glottis and by consequent asphyxia despite medical efforts to save the victim. At autopsy, intense edema and congestion of the pharyngeal, laryngeal, esophageal, and gastric mucous membranes were apparent. Multiple congestions and hemorrhagic suffusion were noticed in all viscera and serous membranes, as well as in the heart and lungs.

Roy et al [56] observed the effects produced by ingestion of 240 ml of 37% formaldehyde in a 41-year-old man. Because of severe stomach pains, the man reported to the hospital within 45 minutes of the draft. Ulcerations were noted in the oropharynx and hypopharynx, and the epiglottis was red and edematous. A tracheostomy was done on the day of admission. The patient was subsequently released, but was readmitted about 6 weeks later because of excessive vomiting, loss of weight, and weakness. Because of stenosis and gastric lesions produced by chemical corrosion, a subtotal gastrectomy was performed, and the duodenum was connected to the small portion of the healthy fundus that remained. The patient recovered but subsequently complained of regurgitation and difficulty in swallowing.

In 1941, Yonkman et al [60] described giving two male subjects 22 mg of pure formaldehyde in water/day for 14 days. Thereafter, every 7 or 14 days the dosage was increased until a dose of 200 mg/day was consumed during the 13th week. Periodic blood samples revealed no significant changes in the concentration of hemoglobin in the red and white cell counts, or in the appearances of these cells. All urine specimens were negative when tested for free formaldehyde and albumin by unspecified methods. One subject complained of mild gastric and pharyngeal discomfort when the formaldehyde reached a concentration of about 0.029%; another voiced similar complaints when a concentration of about 0.04% was attained. This discomfort was alleviated by dilution. The authors also commented that the feeding of formaldehyde-containing foods to rats confirmed the low oral toxicity of this aldehyde.

Corrosive gastritis caused by the accidental ingestion of 100 cc of a solution of formaldehyde was reported by Heffernon and Hajjar [61] in 1964. Severe epigastric pain occurred immediately after ingestion and the patient

collapsed. He awakened several hours later, vomited blood, and passed black stools. Following hospitalization, his general condition improved, but dysphagia continued and he suffered a progressive weight loss of 50 pounds. A subtotal gastrectomy was performed and microscopic study of the specimen confirmed an extensive chemical corrosion of the distal part of the stomach. The patient gradually improved and was discharged, but later had to be treated for a stricture in the esophagus.

In 1968, Bartone et al [62] performed a total gastrectomy on a woman 3 months after she ingested an estimated 120 cc of a 10% solution of formaldehyde. There was an extreme degree of gastric shrinkage, tissue damage, and contracture.

(c) Effects on the Eye

Exposure to airborne formaldehyde [42-47,49-54,63,64] or to airborne dusts carrying absorbed formaldehyde or composed of formaldehyde-yielding materials [44,49,52] has been shown to produce not only respiratory irritation [42-47,49-54] but ocular damage as well. Saury et al [63] observed a case of optical atrophy in a worker employed in a textile factory producing resin-coated fabrics. Ophthalmoscopic examination showed a bilateral papillitis with congestion, but without any edema of the papilla. The condition resulted in repeated short episodes of blurred vision. The authors commented that this optic neuritis was difficult to attribute to occupational intoxication, but that a toxic etiology appeared to be the only one that could be considered seriously.

Schuck et al [64] reported a study of the ocular effects of low concentrations of smog components generated by the photooxidation of either ethylene or propylene within a 520-cu ft smog chamber with welding masks mounted in its sides to allow exposures of human eyes to the atmosphere

within the chamber. Formaldehyde concentrations were determined by a modified chromotropic acid procedure, specific for formaldehyde, with a sensitivity of 0.01 ppm. The subjects reported their feelings of eye irritation in terms of 4 standard descriptions during 5-minute exposures. Exposure to the photooxidation products of ethylene caused somewhat more eye irritation at a given concentration of formaldehyde in the air of the chamber than to those of propylene. The concentration-response relation for subjective irritation of the eyes was linear for propylene oxidation products but became linear for ethylene oxidation products only after concentrations of formaldehyde exceeded 0.3 ppm. The subjects were said to experience equivalent irritations at formaldehyde concentrations of 0.05 and 0.5 ppm. The differences between concentration-response curves for formaldehyde in the presence of the photoxidation products of ethylene and propylene emphasize the importance of other components in the gas mixtures studies. The blinking rate of the eyes, which was used as an objective measure of irritation, was variable for any given subject and passed through several cycles of waxing and waning during a 5-minute exposure period. The authors further reported that the eyes of human subjects could readily detect, by the sensation of irritation, some gas mixtures containing as little as 0.01 ppm formaldehyde.

(d) Skin Effects

Two skin hazards are associated with exposure to formaldehyde: primary irritation [65,66] and allergic dermatitis [43,45,49,67-83]. Primary irritation has resulted from direct skin contact with formaldehyde solutions [65, 66], and exposure to gaseous formaldehyde [65]. Allergic dermatitis has been produced by direct skin contact with formaldehyde solutions [65,68,71, 73,74,78,79], the handling of formaldehyde-containing

textiles [67,69,76,77,80, 81,83], skin contact with formaldehyde from formaldehyde-containing resins [44,65,72,75,82], and exposure to gaseous formaldehyde [43,45,49,65,79,84].

Cases involving primary skin irritation by contact with formaldehyde or its formulations include a case of hyperkeratotic palmar and plantar eczemas in a 63-year-old seamstress who ironed permanent-press cloth with a steam iron [66], dermatitis in a hairdresser who used a hair-waving solution containing 3% formalin (about 1% formaldehyde) [65], red and blistered hands in a pathologist [65], and an irritant dermatitis in fourteen workers using a vegetable glue containing 0.25 - 1% formalin (.09 - .4% formaldehyde). One glue worker after 0.5 - 1 year of exposure became so sensitized that inhaling formaldehyde caused a recurrence of her dermatitis [19]. Patch testing of these people with 4% formalin (1.5% formaldehyde) produced positive reactions. In addition, the seamstress reacted positively to permanent press cotton cloth and reacted slightly to permanent press wool cloth [66]. Pirila and Kilpio [65] also reported observing an irritant dermatitis in two lithographers who handled egg-albumin solutions containing formalin as a preservative. In these incidents of primary skin irritation, repeated exposures to formaldehyde led to development of hypersensitivity in some individuals.

In 1934, Horsfall [79] presented the results of a detailed study of the effects of formaldehyde on a single hypersensitive individual. He investigated cutaneous hypersensitivity, specificity of sensitivity to formaldehyde, cutaneous hypersensitivity reactions after the inhalation of formaldehyde, humoral manifestations, and cutaneous hypersensitivity to formalinized proteins. Following intradermal injections of 0.02 cc, the back of the hand in the subject was found to respond to solutions as dilute

as 1:8,000,000 while the skin of the forearms reacted only to solutions of 1:4,000,000 or less dilution. Aqueous and saline solutions of formaldehyde produced nearly identical results. Horsfall observed a latent period of 15-40 hours between injection and response, which in general was directly related to the amount of formaldehyde injected but had a long plateau between dilutions of 1:640,000 and 1:20,000. In addition, the effects of immersing fingers of either hand, singly or in a pair, in solutions as dilute as 1:8,000,000 were investigated. Here, the greatest dilution producing a positive response was 1:5,000,000 for both the aqueous and saline solutions; latent periods were 16 and 20 hours, respectively for these two solvents. Four control subjects did not react to intradermal injections of 0.02 cc 1:10,000 formaldehyde solutions and three controls had no positive responses to immersion in a 1:1,000 solution. Tests using similar procedures for evaluation of sensitivity to acetaldehyde, propionaldehyde, and paraldehyde produced no positive reactions. In addition, immersions of fingers in solutions of formic acid, hexamethylenetetramine, and methanol failed to elicit any positive reaction. Positive reactions were defined as papules greater than 3 mm in diameter after intradermal injection and swelling of the skin of the finger or fingers, circumferential erythema and itching, and vesiculation after immersion.

Rostenberg et al [68] reported the development of eczematous sensitivity to formalin in five nurses after 2-3 months of handling thermometers kept immersed in a 10% solution of formaldehyde. Papules and vesicles developed on the fingers and, in a few, on the face. When use of the formaldehyde solution was discontinued, the nurses reported no further trouble. Positive sensitivity reactions to formaldehyde were obtained in

all five subjects using patch-testing with formaldehyde solutions from 0.2 to 5% in concentration. The smallest concentration of formaldehyde inducing a positive response was 0.5%; all 5 nurses gave positive responses to formaldehyde at a 5% concentration. Four of the subjects also showed positive reactions after intradermal injections of formaldehyde solutions and formalinized protein. The fifth nurse was not tested in this way. The reactions to injections of formalinized proteins were less pronounced than those to a solution of formaldehyde believed to contain aldehyde in a concentration equal to that in the solution of formalinized human serum albumin.

A case report involving a severe reaction to the formaldehyde component of a nail hardener was published by Lazar [71] in 1966. The distal phalanges in a 58-year-old woman became edematous, red, and scaling, and a bluish discoloration could be seen through the nails. The severe reaction first appeared 2 days after a chemical nail hardener had been applied by a manicurist; no other skin trouble was present. Patch tests with the nail hardener and a 5% aqueous solution of formaldehyde were both positive, producing edema, erythema, and vesiculation. Patch tests with nail polish were negative. Two control subjects did not react to any test materials. The author [71] subsequently observed five other people with similar fingernail damage who had positive reactions to nail hardeners containing formaldehyde. Danto [73] reported a similar effect in a woman whose fingernails became opaque with subungual hyperkeratosis and distal separation from the nail bed following the use of a formaldehyde-containing hardener.

Sneddon [74] reported the outbreak of a sensitization dermatitis in 6 of 13 members of a nursing staff working in a hemodialysis unit. A 2% for-

malin solution was used daily to sterilize the open tanks in which the dialysis solution was prepared. The solution was allowed to stand in the tanks for several hours, during which considerable formaldehyde gas was released into the air of the room. Six months after the opening of the unit, the first case occurred, followed by five others within an unspecified number of weeks. The dermatitis affected the face, neck, arms, and hands. Patch tests with a 3% formalin solution were positive for three of the five nurses; one who did not react when patch tested, later suffered a severe reaction upon accidental exposure, which according to Sneddon confirmed her sensitivity to formaldehyde. With substitution of another sterilizing agent for formalin, all skin lesions attributable to formaldehyde improved. The nurses may have received a mixed cutaneous and inhalation exposure. The type of exposure which was primarily responsible for the observed dermatitis cannot be absolutely identified, but exposure to gaseous formaldehyde seems to be the most likely cause.

Guyot [78] reported that the use of a formaldehyde solution of unknown strength applied to the pulp cavity of a tooth of a 9-year-old boy led to urticaria which disappeared on removal of the solution by flushing the cavity.

Exposure to gaseous formaldehyde [43,45,49,65,74,79] has been implicated as a cause of allergic skin reactions in sensitized people. Lesions observed included drying and reddening of the skin of the face, neck, or arms [43,65,49], and itching eruptions of the face, neck, arms, or hands [45,65,74,79]. In yet another study, Harris [84] reported a tingling of the face and lips with a rapid development of an acute papulovesicular eczema of the whole face, the neck, and the elbow flexures, with subsequent edema of the eyelids and lips, in a man engaged in the breaking up lumps of

a urea-formaldehyde resin. The condition developed after exposure to an atmosphere containing about 30 ppm formaldehyde and recurred after he returned to work.

Individuals sensitized to formaldehyde have been shown to develop allergic contact dermatitis from textiles treated with formaldehyde containing resins [67,69,76,77,80,81,83]. In most cases [67,76,80,81], patients reacted positively to patch tests performed with the resin-treated textiles which were the apparent cause of their dermatitides. In two studies [69,77], patch tests with the textile were negative, but patch tests with formaldehyde were positive. Subjects with latent hypersensitivity to formaldehyde, or with sensitivity to formaldehyde due to causes and sites of application not related to textiles, did not react to the swatches but did react to formaldehyde itself [81].

In contrast to results reported by Peck and Palitz [76], Fisher et al [77] reported in 1962 that formaldehyde-sensitive individuals (12 women and 8 men) did not show any positive skin reaction when patch tested with textiles and paper containing free formaldehyde. Samples of various textiles and papers which had been impregnated with certain formaldehyde resins were tested for free formaldehyde using a method advocated by Marcussen [85]. The resins consisted of urea-formaldehyde, melamine-formaldehyde, and phenol-formaldehyde polymers. All tested samples contained free formaldehyde according to this analytical method.

In 1964, Berrens et al [69] reported analyses of over 600 samples of clothing from patients with nonoccupational formaldehyde contact dermatitis who gave positive patch tests with solutions of 3% free formaldehyde. Very sensitive patients gave positive patch test reactions to 0.3% formaldehyde and some even to 0.03%. Samples of the fabrics were used for patch tests

and also for estimation of formaldehyde content. Nearly 57% of the samples contained less than 0.05% free formaldehyde. Patch tests with these samples were negative. Withdrawal of the clothing made from cloth containing free formaldehyde was followed almost always by disappearance of the dermatitis, however. The authors concluded that patch testing using patients clothing found to contain free formaldehyde is of little clinical value.

O'Quinn and Kennedy [67] noted three cases in which diagnoses of contact dermatitis due to formaldehyde in textiles were established, using the criteria proposed earlier by Fisher [77], the paper or fabric was shown to contain free formaldehyde, the patient gave a positive patch-test reaction to 2-5% formaldehyde a positive patch test was obtained with the formaldehyde resin-impregnated material, and the use or wearing of the fabric or tissue produced clinical dermatitis [67].

In 1966, Shellow and Altman [80] reported the single case of an adolescent man with a 2-year history of a pruritic eruption which began in the antecubital fossae and gradually spread to involve the trunk, extremities, and face. The patient had a history of hay fever and of allergic reactions to 50 commercial allergens. Textiles in his clothing contained free formaldehyde. Although patch tests with some of these textile samples gave positive reactions, others did not.

Skogh [83] noted that 19 cases of formaldehyde eczema in women due to wearing permanent press clothing were all of axillary eczemas. The patients often suffered from recurrences of their conditions, which sometimes spread to other parts of the body. The author reported one typical case in detail. This started with itching under the arms, shortly thereafter, the axillary skin became covered with a weeping, papular rash.

These localized effects reappeared intermittently for about 1 year. Three years after onset, the eczema still persisted and had spread to other areas of the body.

In 1944, Keil and Van Dyck [72] studied 26 cases of nail polish dermatitis in which patch tests with toluene sulfonamide-formaldehyde resin, melamine-formaldehyde resin, toluene sulfonamide-formaldehyde dimer, toluene sulfonamides, and formic acid were performed. The toluene sulfonamide-formaldehyde resin was applied as a 30% solution in acetone. Although no primary irritation occurred in 15 control subjects, 25 of the 26 subjects with a history of nail polish dermatitis gave intense positive patch tests to the toluene sulfonamide-formaldehyde resin; 10 of 11 reacted positively to the malamine-formaldehyde resin, but less vigorously than to the toluene sulfonamide-formaldehyde one. Of 11 subjects with nail polish dermatitis, 8 reacted to the toluene sulfonamide-formaldehyde dimer. By comparison 7 of 16 gave definitely positive reactions to toluene sulfonamide, while only 1 of 13 subjects showed a mild primary irritation to formic acid. These last data are at variance with the idea that hypersensitivity to formaldehyde depends on formation of formic acid.

Kamchatnov and Gayazova [86] studied thermal asymmetry (right side vs left side), measurements of the temperature of the surface of the skin being made on the forehead, the chest, and the forearms, in 99 women, aged 25-40, working in the formalin-using departments of a sheepskin-dyeing factory. An aqueous solution containing 40% formalin solution (500 ml/1), ethanol (250 ml/1), and monochloroacetic acid (40 ml/1) was painted on the sheep skins, which were then calendered with rollers heated to 190-210 C. The air in the breathing zone of the women contained not only gaseous formaldehyde (5-78 mg/cu m) but also methanol vapor (2.1-7.5 mg/cu m), and

ethanol vapor (47.5-110 mg/cu m). In the exposed group of workers, before the start of a shift, 8.3% of the women had equal overall skin temperatures on the two sides of their bodies, 43.3% had "physiological" temperature asymmetry (difference of 0.1-0.5C), and 48.4% had "morbid" asymmetry (difference of 0.6-2.2C). Corresponding percentages for the control group were 69.8%, 27,2%, and 3.0%, respectively. At the end of the shift, the percentages for these types of temperature asymmetry were 7%, 33%, and 60% for the exposed group and 56.9, 34.5, and 8.6% for the control group. These values indicate that exposed women had 3 times the incidence of preshift asymmetry when compared with the controls but that exposure during the shift had a greater proportional effect in shifting workers from the symmetric to the asymmetric state in the control group than in the exposed but produced a greater absolute shift in the exposed group than in the control. Kamchatnov and Gayazova attributed these differences to CNS effects, and complaints of persistent headache, vertigo, and a tendancy to weep were probably related to CNS disturbances as well. No evaluation of possible contribution by methanol or ethanol to the observed effects appears to have been attempted.

Kachlik [87] described an episode involving 63 cases (5.25% of the total number of employees) of occupational skin disorders and irritation of the upper respiratory tract which developed within a 1-year period among employees in a plant processing mainly crease-resistant materials. Complaints were a tightness in the skin, pruritus (particularly of the face), and burning of the eyes and tongue. Redness of the skin and face, swelling of the eyelids, irritation of the throat, and irritation of the nasal mucosa were evident. Free formaldehyde was detected in the fabrics,

lint from which often covered the workers clothing and exposed skin by the end of their shift.

In 1964, Frenk [82] reported the simultaneous appearance in 26 of 120 foundry employees of itching red macules, sometimes with wheal and flare, in or near. the areas of skin rubbed by the clothes. Appearance of these eruptions coincided with periods of inadequate ventilation of the workshop. Frenk thought it likely that these eruptions arose from a combination of mechanical irritation from the foundry dust and a chemical irritation from formaldehyde emanating from furan resins. Both the air and the dust of the foundry were found to contain free formaldehyde.

Logan and Perry [75] reported in 1973 six cases of allergic contact dermatitis from plaster casts containing a melamine-formaldehyde resin. In four of the six patients, a skin reaction developed within 7 days after the application of the resin-containing plaster. In the other two cases, four weeks passed before signs and symptoms developed. The patients all gave positive reactions in patch tests with formaldehyde-containing resins.

Of the numerous additional studies of dermatitis which involved the use or handling of formaldehyde-containing resins [49,70,72,82,88-91], few implicated free formaldehyde as the primary causative agent [49,65,75, 82]. Most concluded that either the parent resin [44,65,70,88-91] or some other substance was the primary causative agent [70,72,82,88,91].

(e) Thresholds of Response

Responses by people to formaldehyde have been by its odor [42,57,58,92-94], upper respiratory tract irritation [42,50, 58], eye irritation [42,46,58,64], and changes in cerebral electrical activity [57,93]. Further, the perception of formaldehyde by odor [58] and eye irritation [46] have been shown to become less sensitive with time as one adapts to formaldehyde.

Aside from the reports described previously [42,58], Leonardos et al [94] have defined the formaldehyde odor threshold to be 1.0 ppm using an odor panel. This threshold represents the lowest concentration to which all 4 trained panelists, selected from a pool of 15 experienced odor panelists, responded positively. At least five different concentrations of formaldehyde were tested.

Freeman and Grendon [92] investigated two laminating plants using four different phenol-resorcinol glues which released formaldehyde upon curing. Air samples were collected at each plant on different days between May 1968 and July 1969 using their modification [92] of the chromotropic acid method following collection of formaldehyde in a fritted gas bubbler containing distilled water. Using a 30-minute sampling period and the modified method, airborne formaldehyde concentrations of 0.04-8 ppm could be determined. Increasing sampling time allows determination of lesser concentrations. Formaldehyde concentrations were 0.04-4.2 ppm in the first plant and 4.2-10.9 ppm in the second. The concentrations varied as a function of the operation of the process at different times of day and of the specific glue being used. The authors reported that employees objected whenever the airborne formaldehyde concentration exceeded 1 ppm, and that the odors in areas found to contain 4.2-10.9 ppm were considered to be unbearable without respiratory protection.

Melekhina [57] subjected 12 persons, aged 19-64, to breathing of various concentrations of formaldehyde in studying the odor threshold and the effects of formaldehyde on the central nervous system. The gas was generated from a glass aspirator, containing 5 ml of formalin through which air was blown. The volume of liquid within the aspirator was kept constant by replacing the formalin as it evaporated. Formaldehyde concentrations

were verified by collection into water in a U-shaped fritted absorber followed by spectrophotometric measurement of the chromophore formed with chromotropic acid. Optical chronaxie determinations were made by using a chronaximeter every 3 minutes during a 15-minute period of breathing formaldehyde-containing air. Optical chronaxie, expressed in microfarads, was measured by the duration of an electrical discharge at a voltage twice the rheobase required to produce the sensation of a flash of light. The airborne formaldehyde concentrations varied from 0.07-1.59 mg/cu m (0.06-1.29 ppm) for each of a large series of tests. Formaldehyde at 0.068 to 0.075 mg/cu m had no effect on rheobase or chronaxie. At 0.084 mg/cu m (0.07 ppm), formaldehyde decreased the chronaxie in two test subjects and increased it in one. Maximal changes for these subjects occurred after breathing formaldehyde-containing air for 9 minutes. This formaldehyde gas concentration decreased the electrical chronaxie from 0.06-0.23 μF. The most pronounced changes were noted at concentrations of 0.2 and 1.59 mg/cu m (0.16 and 1.29 ppm), but for the 3 subjects for whom data are available, two had decreases of 0.10 and 0.22 μF at 0.2 mg/cu m, and of 0.08 and 0.23 μF at 1.59 mg/cu m, whereas the third had increases of 0.09 and 0.39 μF at these two formaldehyde concentrations. The odor panel tests established that 0.11 mg/cu m (0.09 ppm) was the threshold concentration for odor perception of formaldehyde gas for all the test subjects.

In another experiment, [57] the same 12 individuals adapted to a dark, noise-free, odor-free environment during a 5-day training period. Initial curves of responses in receptors in the upper respiratory passages were established for the inhalation of fresh air. They were then exposed to 0.06, 0.07, 0.098, 0.2, 0.3, and 1.7 mg/formaldehyde gas/cu m of air for 4-5 minutes. Under these conditions, the threshold of perception of

formaldehyde by odor was 0.07 mg/cu m for all the subjects. The sensitivity of the eyes to light was increased in 2 subjects by formaldehyde at 0.098 mg/cu m, and was decreased in all 3 subjects tested by formaldehyde at 0.25 to 1.7 mg/cu m.

Fel'dman and Bonashevskaya [93] reported the biologic effects of low airborne concentrations of formaldehyde on humans and rats in 1970. Methods of generation and measurement of formaldehyde concentration were the same as those used by Melekhina [57]. Effects on humans were evaluated by determining olfactory thresholds and changes in cerebral biopotentials. Fifteen healthy human subjects were exposed to formaldehyde at four concentrations between 0.054 and 0.09 mg/cu m. After numerous observations, seven subjects were found to be unable to detect 0.054 mg/cu m of formaldehyde by odor but were able to detect 0.073 mg/cu m of formaldehyde. Four other subjects were unable to detect 0.074 mg/cu m of formaldehyde but were able to detect 0.08 mg/cu m of formaldehyde. The remaining four subjects did not smell 0.08 mg/cu m but could detect 0.09 mg/cu m of formaldehyde. The five most sensitive subjects, as determined by the olfactory threshold tests, were monitored by an EEG during further exposures. A concentration of 0.053 mg/cu m produced statistically reliable ($p \pm 0.05$) changes in cerebral electrical activity in all the subjects, whereas 0.04 mg/cu m produced no effects in any of the subjects. The odor threshold measurements of these authors agree reasonably well with those of Melekhina [57], but EEG appears to be a more sensitive indicator of an effect than either optical chronaxie or the sensitivity to light of a dark-adapted eye used by Melekhina.

Epidemiologic Studies

Several epidemiologic studies involving formaldehyde have described and enumerated cases of dermatitis [84,95,96,97] and upper respiratory tract irritation [47,51,58].

In 1936, Schwartz [95] reviewed the occurrence of dermatitis in the manufacture of synthetic resins. Both phenol-formaldehyde and urea-formaldehyde resin-manufacturing processes described in a companion paper [98] were investigated. Schwartz described one phenol-formaldehyde factory with about 400 employees, where 27 (7%) cases of dermatitis occurred in an 8-month period. Patch tests with powdered hexamethylenetetramine and a 4% formaldehyde solution were positive for 8 of the 10 employees tested from among the 27 cases. Schwartz observed that the dermatitis was more prevalent in winter because then employees did not shower after their shifts. In a urea-formaldehyde resin manufacturing plant, Schwartz reported four (2%) cases of dermatitis, all due to hypersensitivity to formaldehyde, among 190 employees during a 2-year period. In a urea-formaldehyde resin-molding plant, 26 (9%) cases among 300 employees were reported in 10 months of 1934. Half the employees in another urea-formaldehyde resin-molding plant were said to have developed dermatitis in the hot months of 1935. Schwartz believed the observed dermatitis in such cases was due to a mixed exposure involving skin contact with the resins and the inhalation of gaseous formaldehyde. Poor ventilation, poor housekeeping, and a lack of personal cleanliness were also contributing factors.

In a 1943 report based upon studies of seven plants using either urea-formaldehyde or phenol-formaldehyde glues for laminating wood or fabrics, Schwartz et al [96] summarized their observations regarding resin

glue dermatitis. They concluded that the actual cause was complex and that formaldehyde may have been only one of many factors in some cases. In one factory laminating plywood for planes and gliders, 600 (75%) cases of glue dermatitis occurred among 800 employees during the first 6 months of operation. In a factory making tool handles using a phenol-formaldehyde glue, 40 (40%) cases of dermatitis occurred among 100 employees during the first 6 months of operation. No incidence ratios were indicated for the other five plants.

In 1943, Markuson et al [97] studied four industrial plants employing 2,370 employees, 355 (15%) of whom had developed dermatitis because of skin contact with phenol- and urea-formaldehyde resins. The onset of dermatitis usually occurred 3-6 weeks after the initial exposure to the formaldehyde-containing resins. The large majority of employees developed a mild-to-moderate form of dermatitis, characterized by a fine rash, an itching sensation, and redness of the skin. The rash occasionally extended beyond the initially involved area. Recurrence of the same type of dermatitis was common. If contact with the resinous material continued, the exposed skin surfaces, which were already irritated, were subjected to further injury, and a more severe type of dermatitis resulted. Regional distribution was as follows: face, 70%. side of the neck, 73%. chest, 32%, back, 19%, abdomen, 10%, forearms, anterior surface, 72%, posterior surface, 65%, hands, anterior surface, 54%, posterior surface, 62%, legs, anterior surface, 31%, posterior surface, 32%. The investigators concluded that the distribution of the dermatitis on the body surface gave direct evidence of areas in contact with the material while working, or areas touched by hands coated with the resin. Some individuals reportedly developed a mild-to-severe form of skin rash which later subsided. On continued contact with

the resinous material, such individuals generally did not develop dermatitis. The investigators concluded that, if workers should "lose their immunity" at some later period and develop severe dermatitides, the resulting incapacitation would require removal of the employee from working with resins. Occasionally, individuals were reportedly sensitive to formaldehyde itself, so that small amounts of formaldehyde emitted from the resin may have caused the dermatitis. However, the cause of this type of dermatitis, characterized by edema about the eyes and face and marked redness of the face, was not verified by the investigators, but the explanation presented above is consistent with the observations of Harris [84].

Harris [84] reported four (16%) cases of dermatitis among 25 men employed in a small factory manufacturing urea-formaldehyde resin. All 25 had been employed for a minimum of 5 years. All airborne formaldehyde concentrations in the plant were said to be below 30 ppm while in most parts of the plant concentrations were well below 10 ppm, but no details of the type or number of samples or of the analytical method were given. The 25 men had chest radiographs, complete blood counts, and blood pressure readings. Radiographs were completely normal in 14 (56%), signs of old pulmonary lesions were evident in 6 (24%), cardiac enlargement in three (12%), and increased vascular shadows in two (8%). White blood cell counts were elevated in six (24%) men, but those for five of these men (20%) had returned to normal upon recheck. Four of the men complained of mild dyspnea, but one of these had hypertension (blood pressure of 160/115) and another had suffered from asthma for several years.

In 1968, Shipkovitz [58] published the results of a study of eight textile plants in which formaldehyde was released from fabrics treated with

formaldehyde-containing resins. Thirty-two samples for formaldehyde in air were taken with fritted bubblers containing sodium bisulfite and 32 detector tube samples were collected at the same locations. All but two of the detector tube samples failed to detect any formaldehyde (limit of detection either 0.5 or 2 ppm, depending upon which tube was used) and the other two gave considerably different estimates of the concentration of formaldehyde than those obtained from the bubblers. The bubbler solutions were analyzed for total aldehyde by iodometric titration using a method which had a limit of detection of 5 ppm. Airborne formaldehyde concentrations of 0-2.7 ppm, with an average of 0.68 ppm, were reported. Complaints of annoying odor, constant prickling irritation of mucous membranes, heavy tearing, wheezing, excessive thirst, and disturbed sleep were noted. Based upon "composite estimates" obtained from plant records, interviews with foremen, management, and several employees at each plant, the prevalence of respiratory illness and complaints were over 15% at four plants and 5-15% at the other four. The author [58] also mentioned an immediate perception of odor upon entering certain plant areas. Perception would diminish as he spent time in the areas, but would increase again the next day. This account of olfactory acclimatization is consistent with the observations of Sim and Pattle [46].

Other epidemiologic investigations which have been discussed previously under skin effects were the Kerfoot and Mooney [52] survey of funeral homes, the two studies by the California State Department of Public Health [53,54] on formaldehyde in the garment industry, and the Yefremov [47] and Zaeva et al [51] studies of a wood-processing industry.

Animal Toxicity

(a) Metabolism and Retention

Pohl [99] in 1893 administered formaldehyde subcutaneously (sc) to a dog, and sodium hydroxy methane sulfonate, which hydrolyzes to formaldehyde in alkaline solution, also sc, to another dog, and measured the formate excreted in the urine before and after the doses. The first dog excreted excess formate equivalent to about 2.4% of the formaldehyde dose as formate, and the second dog excreted 4% of its potential dose of formaldehyde as formate. There is an apparent minor oxidation of formaldehyde just to formic acid in the dog. In vitro, liver (horse and pig) was found to have a slight ability to oxidize formaldehyde but skeletal muscle (dog) did not. Lutwak-Mann [100] in 1938 and Kendal and Ramanathan [101] in 1952, using in vitro liver preparations, observed that formaldehyde can undergo dismutation to form formic acid and methanol. Malorny et al [102] verified the oxidation to formic acid and formates in vivo in dogs. The latter investigators [102] also showed the possible involvement of liver aldehyde dehydrogenase and nicotinamide adenine dinucleotide (NAD) in this oxidation and further esterification to methyl formate. In vitro experiments [102] with human blood showed that formaldehyde was quickly oxidized to formic acid after its absorption by erythrocytes.

According to Williams [103], the major route of biotransformation of formaldehyde in the body is oxidation to formic acid. He further characterized formaldehyde as a compound which reacts rapidly with the amino groups of proteins and amino acids and presented a plausible scheme of metabolic reactions of formaldehyde. Figure XII-1 shows such a scheme.

In 1972, Egle [104] published a study of the retention of inhaled

formaldehyde in which tracheotomized and untracheotomized mongrel dogs were exposed to formaldehyde at 150-350 ppm in an effort to determine the retentions of formaldehyde in the upper, the lower, and the entire respiratory tract. Formaldehyde gas was generated by forcing air through a formaldehyde solution at room temperature. Samples of gases were analyzed for formaldehyde by the colorimetric method of Sawicki et al [105], using 3-methyl-2-benzothiazolone hydrazone hydrochloride, modified by the addition of sulfamic acid in the oxidizing step [106]. The experiments involved animals inhaling via the nose, through a tightly fitted rubber mask for total-tract experiments and via an endotracheal tube for the lower-tract experiments, and from a spirometer. The animals exhaled into a collection bag. The two types of upper-tract experiments involved severing the trachea just above the bifurcation and passing dilute formaldhyde gas from the spirometer through the tract to this point by means of a mask. In the "1-way" experiments, the vapor passed into a collecting bag at the lower end of the trachea and was not returned, whereas in the "2-way" experiments the vapor was returned upward by means of a 2-liter syringe attached to the lower end of the trachea. At least four dogs were used in each type of experiment.

The total-tract retention was nearly 100% regardless of the ventilatory rate, formaldehyde concentration or tidal volumes measured. In the 2-way upper tract retention studies, the uptake of formaldehyde was 100% at all rates. The retention of formaldehyde was slightly lower with a single pass through the upper tract, but still exceeded 95%. The results of exposure of the lower tract alone showed over 95% uptake of formaldehyde. Thus, for the range of concentrations studied, both the

upper and the lower parts of the respiratory tract were shown to be effective absorbers of formaldehyde.

(b) Acute Exposures

The LD50 for formaldehyde was shown by Skog [107] to be 300 mg/kg in mice, and 420 mg/kg in rats following sc injections of 150-460 mg/kg in 72 mice and 300-640 mg/kg in 64 rats. Skog further found the LC50 of formaldehyde for rats to be 1000 mg/cu m (810 ppm) air based upon 30-minute exposures at 600-1,700 mg/cu m (490-1400 ppm) in a total of 72 rats. These values were determined in groups of eight animals for each dose (mg/kg body weight or mg/cu m of air). The exposure time for inhalation was 30 minutes. The animals were kept under observation for up to three weeks after completion of exposures. Determinations for gaseous formaldehyde in air were made as total aldehydes, using a method based on the sodium sulfite reaction. The formaldehyde solutions used had the following concentrations: for injections, 35.5% for rats and 2% for mice; for inhalation, 35.5% for rats and mice.

With subcutaneous administration, the animals became listless and showed lacrimation and increased secretion from the nose. Respiration was accompanied by a whining and rattling sound; with each breath the animals gaped and turned their heads backward. All deaths of rats occurred within 68 hours, and those of the mice within 20 minutes. The survivors recovered after 2-3 days. Autopsy findings were bronchitis and slight pulmonary hyperemia with small hemorrhages and edema being visible around some vessels. Hyperemia was noted in the liver and kidneys also, with no changes in other organs.

Signs which appeared after SC administration appeared also after inhalation and were considerably more pronounced. Respiratory difficulty

lasted several days after exposure and, in some rats, for as long as 2 weeks afterwards. The last death occurred on the 15th day after the exposure. Microscopic changes in the lungs included hemorrhages and intra-alveolar and perivascular edema. Hyperemia, perivascular edema, and necroses were found in the livers; perivascular edema was found in the kidneys. No changes were noted in other organs. (The rat that died on the 15th day had also purulent bronchitis and diffuse bronchopneumonia.)

In 1911, Iwanoff [108] exposed 2 groups of 2 cats each and 1 group of 3 cats to increasing concentrations of formaldehyde. As seen in Table XII-6, formaldehyde concentrations of 260-820 mg/cu m (211-667 ppm) for 3.5-hours produced temporary irritation of the mucous membranes and slight dyspnea in both cats, which recovered after 2 days. The two cats exposed to 820 mg/cu m (664 ppm) for 8-8.7 hours died on days 4 and 6, respectively, after profuse salivation, pronounced dyspnea, and vomiting. The three cats exposed at 2,010-9,630 mg/cu m (1628-7800 ppm) for 3-4.7 hours died. One died during the exposure; another died 20 minutes after the end of the exposure; and the third died 4 days later. All three experienced hypersalivation, pronounced dyspnea, vomiting, and general cramps. At autopsy, the five cats in the two higher-exposure groups had pulmonary edema, hyperemia, and hemorrhages of the lungs, pus in the trachea and bronchi, and hyperemia of the kidneys.

Carpenter et al [109] exposed groups of six Sherman strain rats weighing 100-150 g to formaldehyde, for periods of 4 hours and observed the death rates in these groups for 14 days. Calculated airborne formaldehyde concentrations were generated from a formalin solution introduced into a heated tube at a constant rate from a motor-driven syringe, air being passed through the tube in a countercurrent direction and into the exposure

chamber. No analysis of chamber air was made. Exact details of death were not given, but exposures to formaldehyde at 250 ppm killed 2, 3, or 4 of the 6 rats in the exposed groups prior to the end of the observation period.

Murphy et al [110] exposed eight rats to formaldehyde at 35 ppm for 18 hours. The formaldehyde concentrations were generated by metering the gases through a dilution system and into a chamber ventilated at the rate of 2 cubic feet/minute. Air concentrations of formaldehyde in air were verified by the method of Altshuller et al [111]. A control group of eight rats received clean air only. All animals in both groups were killed 24 hours after the start of exposure, and their organs were subjected to gross pathologic examination and biochemical analysis. As seen in Table XII-6, the exposed rats had dyspnea, eye and nasal irritation, and significantly higher ($p \pm 0.01$) liver alkaline phosphatase activities than the controls.

In 1960, Salem and Cullumbine [112] reported a study of the inhalation toxicity of formaldehyde for 2 groups each of 50 mice, 20 guinea pigs, and 5 rabbits. The animals were exposed for up to 10 hours in a 1 cu-m dynamic chanber made of plate glass. One group was exposed to formaldehyde at 20 mg/cu m as an aerosol of formalin and the other group to formaldehyde at 19 mg/cu m as a gas. The aerosol had a mean particle diameter of 0.7 μm. The formaldehyde gas was introduced into the same apparatus by gentle bubbling of air through formalin, which was held at 50 C in a water bath. Aerosol and gas concentrations were analyzed quantitatively after sampling into impingers containing hydroxylamine hydrochloride. As summarized in Table XII-6, 48 (96%) of 50 mice died during or shortly after exposure to the aerosol while 17 (34%) of the 50 mice exposed to the gas died during a similar time period. Only 1 (5%) of

the 20 guinea pigs exposed to the aerosol died, but 8 (40%) of those exposed to the gas succumbed. One (20%) of the rabbits exposed to the aerosol died while three (60%) of those rabbits exposed to the gas were killed. At autopsy, all animals had expanded, edematous, and hemorrhagic lungs with distended alveoli, and most had ruptured alveolar septa.

In two studies [113,114], Amdur exposed guinea pigs for periods of 1 hour to formaldehyde at various concentrations and other irritants with and without simultaneous exposure to an aerosol of NaCl. Intrapleural pressure, tidal volume and into and out of the respiratory system were monitored by the methods of Amdur and Mead [115]. A dynamic exposure chamber was used for all exposures. Concentrations of formaldehyde in air were prepared by passing air through a sintered glass bubbler containing a 37% formaldehyde solution and diluting the resultant stream with air prior to introduction into the chamber. The aerosol of NaCl was generated by aerosolizing a 1% NaCl solution in a Dautrebande generator. The formaldehyde concentrations were measured by the Schiff's reagent method suggested by Elkins [116], or, for low concentrations, by the chromotropic acid method of MacDonald [117]. The geometric mean particle size of the NaCl aerosol was found by electron microscopy to be 0.04 μm with a geometric standard deviation of 3.3. The concentration of NaCl in the aerosol was determined by collection on a membrane filter, followed by soaking in demineralized water and measurement of the conductivity of the water. When the aerosol was used in combination with the formaldehyde, the filter preceded the midget impinger used for gas sampling. According to Amdur [113], an increase in the product of resistance and compliance suggested that bronchial constriction was the principal response to formaldehyde. When three guinea pigs were exposed to 50 ppm formaldehyde

for 4 hours [113], the resistance increase produced by formaldehyde reached its maximum by the end of the first hour of exposure. During the second hour, the resistance decreased slightly, and then remained constant during the remaining 2 hours. Two hours after the end of the exposure, the resistance had decreased markedly but had not returned to the control value. Exposure to formaldehyde increased the amount of work required to overcome the increased elastic, resistive, and elastic plus resistive components of ventilatory recoil.

Amdur experimented further [113] by exposing normal and tracheotomized guinea pigs to formaldehyde and to formaldehyde in the presence of NaCl aerosol to bypass the scrubbing effect of the upper respiratory tract and study the effect of more direct access by formaldehyde to the lung parenchyma. A greater response was obtained for formaldehyde gas alone at a particular atmospheric concentration when the protective effect of the upper airway was eliminated. Untracheotomized animals exposed to formaldehyde and NaCl aerosols had additive effects of exposure. Figure XII-2 shows the effects of exposure to formaldehyde in combination with NaCl aerosols. The greatest changes were observed in tracheotomized animals receiving both formaldehyde and NaCl aerosol. All responses within an exposure group were proportional to the concentrations of formaldehyde, however.

In a second report [114], Amdur exposed normal guinea pigs to formaldehyde alone and to formaldehyde with NaCl aerosol, and tracheotomized guinea pigs to formaldehyde as above in concentrations from 0.9 to 50 ppm. In addition, the effects of adding the NaCl aerosol to the formaldehyde at various exposure concentrations were investigated. Methods used to generate formaldehyde and NaCl aerosol concentrations and

techniques used to measure responses were identical with those previously used [113]. The results of these experiments, summarized in Table XII-10, were observations of increased resistances and decreased compliances after exposures to formaldehyde at 0.9, 5.2, 20, and 50 ppm and combined exposures to formaldehyde at 1.1 and 3.6 ppm in the presence of an aerosol containing 10 mg NaCl/cu m. Tidal volumes were unchanged by the exposures in all groups except those receiving formaldehyde at 5.2, 20, and 50 ppm and those receiving formaldehyde at 3.6 ppm in the presence of NaCl aerosol. Elastic work was increased significantly only in the group exposed to formaldehyde at 50 ppm.

As indicated in Figure XII-2, the conclusions made in Amdur's previous report [113] remained unchanged. The dose-response curves indicated that resistance was increased in accord with the concentration of formaldehyde, and that addition of aerosolized NaCl may have increased the effectiveness of formaldehyde in heightening resistance. Those untracheotomized guinea pigs receiving formaldehyde plus the aerosol were more severely affected than tracheotomized animals receiving formaldehyde alone, which, in turn, were more severely affected than untracheotomized animals receiving formaldehyde alone [113,114].

Murphy and Ulrich [118] subjected 10 and 9 guinea pigs to 1-hour exposures to formaldehyde at concentrations of 3.9 and 12.5 ppm, respectively, and monitored resistance to airflow, respiratory rate, and tidal volume. Formaldehyde concentrations were generated by an unspecified method and were introduced via a manifold through masks to individual guinea pigs housed in exposure-pneumotachygraph chambers, which restricted their movements. A plethysmograph was used to record respiratory rate and tidal volume. Total respiratory resistance to airflow was determined from

the plethysmograph record and flow-calibrated pressure changes in the mask of each animal. Sequential measurements of respiratory rate, tidal volume, and resistance during expiration and inspiration were taken at 15-minute intervals and were reported as the average percentage of preexposure values. Formaldehyde concentrations of 3.9 and 12.5 ppm, as shown in Table XII-6, increased resistance to airflow by 69% and 81%, respectively, increased tidal volume by 29% and 36%, and decreased the respiratory rate by 27% and 37%.

In 1967, Davis et al [119] studied the respiratory effects during exposure of guinea pigs to airborne formaldehyde. Continuously measured responses included intrapleural pressure, respiration rate, and tidal volume in intact and tracheotomized animals. Formaldehyde was determined by the chromotropic acid method of Altshuller et al [120]. A t-test of paired data was used for statistical analysis, since each animal acted as its own control. Qualitatively continuous exposure for 60 minutes to formaldehyde at 50, 1,000, and 6,000 ppm resulted in increases in resistance, decreases in respiration rate, increases in tidal volume, decreases in minute volume, and no changes in compliance. In tracheotomized animals, formaldehyde did not produce changes in any of these areas. This data is summarized in Table XII-6. The authors concluded that these irritant responses were nonspecific and due to receptors present in the nasopharynx and larynx of the guinea pig which are stimulated by irritant and chemically inert substances, e.g., formaldehyde.

(c) Chronic Exposure

Coon et al [121] continuously exposed animals for 90 days via inhalation to formaldehyde at 4.6 mg/cu m by bubbling air through a 1.35% formaldehyde solution into modified Rochester-type exposure chambers.

Airborne formaldehyde concentrations were monitored continuously with a nondispersive infrared analyzer. Five species, including "15 male and female Sprague-Dawley and Long-Evans-derived rats, 15 male and female Princeton-derived guinea pigs," 13 male New Zealand albino rabbits, 3 male squirrel monkeys, and 2 purebred male beagle dogs were exposed to formaldehyde in the chambers. An unspecified number of control animals were maintained in similar dynamic chambers without contaminants and were handled in the same way as the experimental animals. As shown in Table XII-6, one of the 15 rats died during the continuous formaldehyde exposure, but none of the other animals showed any clinical signs of illness or toxicity. Hematic values were normal. On microscopic examination, the lungs of all species of exposed animals consistently showed varying degrees of interstitial inflammation, and the hearts and kidneys of guinea pigs and rats had focal chronic inflammatory changes. The investigators were uncertain whether these changes resulted from the inhalation of formaldehyde. Details of the microscopic examination of tissues and organs from the control animals were not reported.

In 1970, Fel'dman and Bonashevskaya [93] reported the effects of low airborne concentrations of formaldehyde on rats. Four groups of 25 male albino rats were exposed continuously for 3 months to air containing formaldehyde at 0.012, 0.035, 1.0, and 3.0 mg/cu m (0.0098, 0.029, 0.82, and 2.45 ppm) in a 100-liter dynamic exposure chamber. A fifth group of 25 served as controls. Microscopic studies of the lungs of animals exposed to formaldehyde at 1 and 3 mg/cu m (0.81 and 2.43 ppm) revealed proliferation of lymphohistiocytic elements in the interalveolar walls and in the peribronchial and perivascular spaces, against a background of moderate hyperemia. The liver exhibited nuclear polymorphism, a profusion of

binuclear cells around the triads, focal hyperplasia and activation of the elements of the reticuloendothelial system. At the same time, the liver cells exhibited a moderate decrease in glycogen content and enlargement and rarefaction of RNA granules. The kidneys of rats in the groups exposed to formaldehyde at 1 and 3 mg/cu m exhibited somewhat dilated vessels in the juxtamedullary zone of the cortex. The parietal area of the cerebral cortex exhibited focal proliferation of the glial elements, with many satellites of oligodendrocytes and astrocytes. No structural histologic changes were in noted groups exposed to formaldehyde at lower airborne concentrations. No further details regarding the methods of generation of formaldehyde or of its analysis were reported.

Carcinogenicity, Mutagenicity, and Teratogenicity

Horton et al [122] in 1963 published a study in which mice with lower than usual incidence of pulmonary adenomas were exposed to inhalations of formaldehyde and coal tar at various concentrations in aerosols in an effort to determine whether formaldehyde would induce bronchogenic carcinoma, predispose mice to cancer if they were exposed to only enough to produce metaplasia of squamous epithelial cells, or render exposed animals more susceptible to cancer of the skin or lungs than control animals upon exposure to coal tar aerosol. Formaldehyde concentrations were generated in a 623-liter chamber from a heated 2:1 mixture of paraformaldehyde and white mineral oil through which air was aspirated and subsequently diluted with make-up air. The actual formaldehyde concentrations in the chamber were analyzed quantitatively prior to each exposure and at 30-minute intervals by a modification of the bisulfite method of Goldman and Yagoda

[123], in which sodium bisulfite was used instead of thiosulfate for the destruction of excess iodine. Coal tar aerosol was generated from a heated glass and stainless steel generator pressurized with preheated nitrogen, with subsequent cooling to 27-28 C and dilution with air prior to entry into the inhalation chamber. Particulate matter in the air of the chamber was collected periodically on a filter and analyzed for benzo(a)pyrene by the method of Tye et al [124]. Both the coal tar and the aerosol generated were found to contain 0.71% benzo(a)pyrene in terms of total tarry material.

In preliminary range-finding experiments, Horton et al [122] found that exposure of mice to formaldehyde at 900 mg/cu m (731 ppm) for 2 hours caused death from pulmonary hemorrhage and edema. Further tests at 40 mg/cu m (32 ppm) formaldehyde for 2 hours/day for 4 days failed to kill any of the test animals and produced no "substantial" distress or weight loss.

Following the range-finding experiments, another batch of mice was divided into five groups. One group of 59 mice received no formaldehyde exposure for 35 weeks; 26 were then killed for microscopic examination of lung sections. The remaining 33 mice were exposed to coal tar aerosol at 300 mg/cu m for 2-hour periods, three times/week, for 35 weeks. A second group, of 60 mice, was exposed to formaldehyde at 50 mg/cu m (41 ppm), 1 hour/day for 35 weeks, when 23 were killed for microscopic examination of lung sections. The 37 remaining mice were exposed to formaldehyde at 150 mg/cu m (122 ppm) for the next 35 weeks. During that time, one mouse died from causes unrelated to the experiment. A third group, of 60 mice, was exposed to formaldehyde at 100 mg/cu m (81 ppm), 1 hour/day, for 35 weeks. Thirty-four were then killed for microscopic examination. The remaining 26 were exposed for 2-hour periods, three times/week, for 35 weeks to coal tar

aerosol at 300 mg/cu m. A fourth group, of 42 mice, was exposed a total of 11 times to formaldehyde at 200 mg/cu m (162 ppm) during a 4-week period, when the 35 surviving mice were killed for microscopic examination. Mice in the fifth group served as controls and were killed after 82 weeks. Early structural changes in respiratory tissue were observed, but no tumors were found. Further, preconditioning with sufficient formaldehyde to produce irritation of the airway did not predispose mice to pulmonary or epithelial cancer from subsequent exposure to coal tar aerosol.

In 1966, Gofmekler [125] carried out inhalation experiments in which pregnant rats were continuously exposed to formaldehyde. Three groups of 12 female rats each were placed in chambers in which they were exposed to formaldehyde for 10-15 days before impregnation. They were then caged with males for 6-10 days, taking into account the 5-day sexual cycle of the females. The average length of pregnancy was 22 days. Two groups were exposed to concentrations of formaldehyde of 1 mg/cu m (0.8 ppm) and 0.012 mg/cu m (0.01 ppm), respectively. Both groups showed evidence of affected embryonic development in that the mean duration of pregnancy was increased by 14-15% over that of the third group of 12 controls. There were 135 fetuses in the control group, 235 in the 0.012 mg/cu m exposure group, and 208 in the 1.0 mg/cu m exposure group. Total body weight and the weight of the adrenal glands for offspring of the dams exposed to formaldehyde at both concentrations were greater than those of the offspring of the control dams. The weights of the kidneys and thymus of the offspring from females exposed to formaldehyde at 1.0 mg/cu m were also greater than those of the offsprint of the control dams. In contrast, the lung and liver weights of the offspring of both exposure groups were less than those of offspring of the control group.

Formaldehyde can react with hydrogen chloride and inorganic chlorides to yield bis-chloromethyl ether (BCME) [7,126-131], which is a potent carcinogen according to 29CFR 1910.1008. The reaction occurs at high concentrations (500-3,000 ppm) of formaldehyde and chlorides [128] but Tou and Kallos [132] reported that at the low concentrations encountered in the industrial environment, no evidence of formation of BCME using several common chloride salts could be found when using an analytical method with a detection limit in the low parts per trillion range.

Correlation of Exposure and Effect

Principal hazards which have been associated with human exposure to airborne formaldehyde are irritation of the respiratory tract [29,30,42-52,58], of the eye [42-45,47,67-69,71-73,84], and of the skin [65,66]. The effects on the skin may be particularly offensive in individuals who have become sensitized to formaldehyde by prior exposure or by other means [43-45,47,67-69,71-73,84]. In addition, the odor of formaldehyde is perceptible and may be disturbing to individuals unaccustomed to it at concentrations of the aldehyde which will vary from one individual to another. These concentrations are generally at or below 1 ppm [42,92], 57,58,93,94]. Acute irritation of the human respiratory tract from inhalation of formaldehyde has caused pulmonary edema [27,48], pneumonitis [59], and death [27]. Damage to the lungs in animals, as seen in Table XII-6, has been found on exposure to formaldehyde at much lower airborne concentrations [93,110,112,113,121, 114,119,122,125]. Two cats were killed by inhalation of formadelhyde at about 667 ppm in 4 and 6 days, respectively [108]. As seen in Table III-1, irritation of the upper

respiratory tract has been reported in workplaces with formaldehyde concentrations between 0.09 and 11 ppm [42-44,47,51,52,54]. Other studies [43,44,47,50-52,54] support the possibility that aldehyde concentrations of 1-2 ppm may be irritating to some individuals. This effect is evidently somewhat independent of becoming accustomed to it because some investigators [52,54,58] have noted that, although initial irritation subsides to some extent after 1-2 hours of exposure, it returns again after a lunch period or a time away from the workplace.

In addition, Russian investigators have noted altered visual sensitivity [51, 93] and changes in cerebral electrical activity in a preselected group exposed to formaldehyde at 0.8 ppm [93]. Moreover, other Russian investigators [57] have reported optical chronaxie changes after inhalation of formaldehyde for 9-10 minutes at concentrations from 0.07 to 1.3 ppm among individuals preselected on the basis of perceiving the odor of formaldehyde at a concentration of 0.06. Although detection of formaldehyde is possible apparently by some people by unusual means (altered chronaxie of the optic nerve), the application of this information to control of industrial exposures to formaldehyde is uncertain at present.

Once skin sensitization to formaldehyde has occurred, exposures to as little as 10.5 ppm for 10 minutes have caused definite skin reactions [79]. Furthermore, a slight reddening and drying of the skin has been noted in a group of employees with airborne exposure to less than 4 ppm formaldehyde [43]. In this case, however, the possibility of direct skin contact as a causal factor cannot be excluded.

Considering differences in body weights and respiration rates, animal data, summarized in Table XII-6, appear to support the observations made in humans with respect to the effects of airborne exposures to formaldehyde,

but indicate adverse reactions in animals from exposures to formaldehyde at generally lower air concentrations than those that affect humans similarly. Formaldehyde at a concentration of 49 ppm for 1 hour, caused airway resistance changes in guinea pigs which persisted for more than 1 hour after cessation of exposure, whereas exposure to formaldehyde at 11 ppm for 1 hour produced transient changes in resistance to the flow of air into and out of the lungs which disappeared within 1 hour of cessation of exposure [113,114]. Monkeys, rabbits, guinea pigs, rats, and dogs exposed to concentrations of 3.7 ppm for 24 hours/day for 90 days developed interstitial inflammation of the lungs [121]. Slight changes in the structure of the lungs have been found after exposure of cats to as little as 0.8 ppm [93]. Amdur [113,114] found airway resistance changes after exposing guinea pigs to as little as 0.31 ppm formaldehyde for 1 hour. Such changes were more dramatic when aerosolized saline solutions were included with the formaldehyde in the atmosphere within the exposure chamber [114], as seen in Figure XII-2. Changes of airway resistance were observed in such experiments after 1 hour exposure to formaldehyde at as little as 0.11 ppm in the presence of an NaCl aqueous aerosol with a mass median diameter of 0.04 μm and a NaCl concentration of 3.9 mg/cu m [114]. Following continuous 24 hour/day exposure of pregnant rats to formaldehyde concentrations as low as 0.01 ppm, a change in gestation time and both increases and decreases in the organ weights were reported [125]. There was also an increase in litter size in comparison with that of controls.

There is no evidence that formaldehyde is a carcinogen [133], but it has produced some effect on rat fetuses [125]. The significance of observed increases in organ weights for the rat fetuses requires further study. BCME apparently does not form in detectable amounts (ppt) at the low concentrations found in industrial environments [132].

The principal hazards of formaldehyde [65,66,68,71,73,74,78,79] or formaldehyde-yielding substances [44,65,67,69,72,75-82,95,98] to the human skin are either primary irritation [65,66] or allergic contact dermatitis [65,68,71,73,74,78,79]. Primary irritation has been elicited when human skin has contacted solutions as dilute as 4% formaldehyde [65,66], while one sensitized individual showed an allergic reaction to formaldehyde solutions as dilute as 1:8,000,000 when 0.02 cc was injected intradermally or when fingers were immersed for 40 minutes in a 1:5,000,000 solution [79].

Tissue destruction produced by ingestion of formaldehyde has been demonstrated in accidents [22-24,55,61], in human experimental feeding studies [85, 60], and in attempted suicides [24,56,62]. Table III-2 shows that the ingestion of as little as 50 mg of formaldehyde was fatal to a 3-year-old child [22] while 330 mg caused the death of an adult [22]. Furthermore, an experimental dose of 100-200 mg taken daily in milk produced headache, stomach pain, a burning sensation in the throat, and a rash in 4 of 11 subjects so tested [19]. The rash could well have been due to prior sensitization. Gastric and pharyngeal discomfort were also reported from daily ingestions of 22-200 mg formaldehyde by another group [60].

To date, no LC50 for formaldehyde has been estimated for humans, although there have been at least two accidental deaths, one from a massive inhalation [41] and the other from inhalation of an uncertain amount [27]. Animal studies have shown a 30-minute LC50 of 1000 mg/cu m (810 ppm) for rats [107], and LD50's by subcutaneous injections of 0.30 g/kg for the mouse [107] and 0.42 g/kg for the rat [107]. However, inhalation studies have shown that 17 of 50 mice [112], 8 of 20 guinea pigs [112], and 3 of 5 rabbits [112] were killed by a 10-hour exposure to formaldehyde at a

concentration of only 15.4 ppm. The lowest concentration of formaldehyde reported to kill 1 rat out of 15 was an inhalation of 3.7 ppm, to which rats were exposed 24 hours/day for 90 days [121]. However, death of this rat may have been due to other causes since there was no satisfactory evidence (gross and microscopic examinations) that changes typical of those induced by formaldehyde were responsible for the animal's demise. Because of insufficient data, one can conclude only that any concentration immediately hazardous to life would be an unbearable respiratory and eye irritant to any unprotected individual.

TABLE III-1

DOSE-RESPONSE RELATIONSHIPS FOLLOWING HUMAN EXPOSURE TO AIRBORNE FORMALDEHYDE

Concentration (ppm HCHO)	Duration of Exposure	N	Responses	Reference
41.7	10 min	1	Bilateral vesicle reaction on hands of hypersensitive person	79
16-30	8 hr/d	60	Eye and throat irritation, skin reaction	49
±10-30	Min	1	Skin and eye tingling in hypersensitized worker, progression to generalized skin reaction	84
13.8	30 min	12	Nose and eye irritation subsiding after 10 min in chamber	46
1-11	8 hr/d	>50	Eye, nose, and throat irritation	4
4.2-10.9	Min		Unbearable without respiratory protection	19
10.5	10 min	1	Bilateral vesicle reaction on hands of hypersensitive person	79
0.5-7.3	Daily	278	Increased occurrence of upper respiratory irritation	47 51
± 4 ?		Several	Complaints of irritation of conjunctiva, nasopharynx, and skin; increased incidence of catarrhal conjunctivitis, slight reddening and drying of the skin	3
0.09-5.26 (with paraformaldehyde)	Hr	"	Eye and upper respiratory irritation; lessened during day, returned after lunch or next day	52
0.3-2.7	8 hr/d	"	Annoying odor, constant prickling irritation of the mucous membranes, disturbed sleep, thirst, heavy tearing (Odor subsided during day, but returned at start of next shift)	58

TABLE III-1 (CONTINUED)

DOSE-RESPONSE RELATIONSHIPS FOLLOWING HUMAN EXPOSURE TO AIRBORNE FORMALDEHYDE

Concentration (ppm HCHO)	Duration of Exposure	N	Responses	Reference
0.9-2.7	Hr	"	Tearing of eyes and irritation of nasal passages and throat (Irritant effects were greatest at very beginning of workday and after lunch)	54
0.9-3.3	Hr	Several	Mild eye irritation, objectionable odor	53
0.9-1.6	8 hr/d	2	Itching eyes, dry & sore throats, disturbed sleep, and unusual thirst upon awakening in the morning	50
1.0	Odor panel	4	Odor threshold	94
1.4	Min	12	Eye sensitivity to light lowered in unacclimated group	57
0.06-1.3	"	12	Optical chronaxy changes in unacclimated group	57
> 1.0	"	Several	Increased worker complaints	19
0.8	"	12	Altered functional state of cerebral cortex	93
0.8	Daily	?	Equilibrium and olfactory sensation shifts; irritation of upper respiratory tract and eyes in most sensitive individuals; enhancement of alpha-rhythms	51
0.3-0.5 (smog chamber)	5 min (eye only)	12	Increased blink rate, rate proportional to formaldehyde concentration	64
0.05-0.5 (smog chamber)	"	12	Eye irritation range in unacclimated group	64

TABLE III-1 (CONTINUED)

DOSE RESPONSE RELATIONSHIPS FOLLOWING HUMAN EXPOSURE TO AIRBORNE FORMALDEHYDE

Concentration (ppm HCHO)	Duration of Exposure	N	Responses	Reference
0.13-0.45	?	Several	Complaints of temporary eye and upper respiratory tract irritation	2
0.07	Min	15	Odor perception threshold for group	2
0.06	Min	12	"	57
0.05	"	5	No alteration of cerebral electrical activity in subjects most sensitive to odor	93

TABLE III-2

DOSE-RESPONSE RELATIONSHIPS FOLLOWING THE INGESTION OF FORMALDEHYDE BY HUMANS

Amount of HCHO Ingested (mg)	N	Time Before Treatment	Responses	Reference
10,000 (100 cc)	1	Several hr	Severe epigastric pain, passed black stool; dysphagia, stenosis and corrosive destruction of the stomach	61
8,800 (240 ml of 37%)	1	45 min	Severe pain, ulceration and stenosis of stomach, dysphagia	56
50-8214 (Few drops to 7.5 oz)	12	Various	Gastrointestinal pain, corrosion of tissues of contact organs, respira-	22
6,000 (150 ml of 40%)	1	Immediate	Death, edema of glottis, asphyxia	55
2,200-2,400	1	45 min	Cyanosis; low temperature; shallow respiration; weak, rapid and irregular pulse	24
1665 (1 1/2 oz formalin)	1	1 hr	Cyanosis, vomiting, dry mucous membranes in mouth and throat, weak and irregular pulse, shallow respiration	24
1200 (120 ml of 10%)	1	?	Gastric shrinkage and contracture after 3 mo	62
555-600 (0.5 ml of 37-40%)	1	24 hr	Coma, recovery with treatment	23
555-600 (1/2 oz formalin)	1	?	Dry and sore throat, vomiting	24
100-200 daily in milk for 3 weeks	11	--	Headache, stomach pain, burning sensation in throat, rash on chest and thighs in 4 of the 11	19
22-200 daily	2	--	Mild gastric and pharyngeal discomfort	60